REMARKS

The present application is directed to methods for detecting cancer by combining mammalian autoantibodies with a patient sample to determine whether cancer-associated marker proteins are present in the sample. The autoantibodies demonstrate a superior affinity for cancer-associated marker proteins, thereby enabling early cancer detection and the ability to commence treatment and enhance cancer patient survival.

Claims 1, 59, 60 and 66 have been amended to more particularly point out and distinctly claim the subject matter which applicants regard as their invention. Claims 5-51 have previously been cancelled. Upon entry of this amendment, Claims 1-4 and 52-66 will be pending.

Summary of Interview with Examiner

Applicants wish to thank the Examiner for her time and consideration during the personal interview with one of the inventors of the above-referenced patent application, John Robertson, and applicants representative, Jamie Greene, on June 6, 2005. During the interview, applicants discussed prospective amendments to the claims and the differences between the claimed method and the prior art (Rao *et al.*, *Proceedings of the American Association of Cancer Research Annual Meeting* 28:358 #1419, 1987; Rao *et al.*, *Am J Obstet Gynecol* 159:94-98, 1988; and Houghton *et al.*, *J Exp Med* 158:53-65, 1983).

As indicated on the Interview Summary, the Examiner has stated that the claimed method distinguishes over the prior art because the claimed method is more specific and sensitive for the detection of cancer-associated modified forms of wild-type proteins.

Rejections under 35 U.S.C. §112, first paragraph

In the Office Action mailed February 11, 2005, the Examiner rejected Claims 59 and 60 under 35 U.S.C. §112, first paragraph, for lacking enablement on the basis that antibodies are produced by B lymphocytes or B cells, not monocytes, which were recited in these claims.

Applicants have corrected this clerical error by amending Claims 59 and 60 to replace the word "monocytes" with the word "mononucleocytes". A corresponding correction was made on page 8 of the specification. Support for these amendments can be found in Example 1 on pages 11 and 12 of the specification. In view of the amendments, applicants respectfully request withdrawal of this rejection.

Rejections under 35 U.S.C. §102

In the Office Action mailed February 11, 2005, the Examiner rejected Claims 1, 3, 4, 52, 53, 54, 62, and 66 under 35 U.S.C. §102 as being anticipated by Rao *et al.* (*Proceedings of the American Association of Cancer Research Annual Meeting* 28:358 #1419, 1987; "the Rao abstract"). Applicants respectfully submit that the amendments to the claims overcome the rejection.

As discussed with the Examiner during the interview on June 6, 2005, Claims 1 and 66 have been amended to clarify that the antibodies in the detection method are autoantibodies to a cancer-associated marker protein that is a **modified form of a wild-type protein**.

The Rao abstract describes the isolation of IgG complexes from the ascites fluid of patients with ovarian cancer, dissociation of the complexes, purification of the antibodies dissociated from the complex by ion-exchange chromatography, and reaction of the purified antibodies with blood sera from cancer patients. No data is shown.

In order to more fully understand the teachings of the Rao abstract, applicants obtained a copy of a subsequent scientific paper by Rao and Hanjani entitled, "Detection of human ovarian tumor-associated antigens by antibodies isolated from ovarian carcinoma ascitic fluid", *Am J Obstet Gynecol* 159:94-98, 1988; "the Rao paper". This paper was disclosed in a Supplemental Information Disclosure Statement filed May 6, 2005. The Rao paper describes the isolation of IgG complexes from the ascites fluid of eight patients with stage III (primary) epithelial carcinoma of the ovaries, dissociation of the IgG complexes, and purification of the antibodies dissociated from the IgG complex by ion-exchange chromatography. The Rao paper further describes the isolation of "free antigens" from the blood

sera of ten patients with stage III ovarian epithelial cancer by heat inactivation of the serum samples, passage of the heat inactivated serum through a Protein A Sepharose column to bind IgG and IgG complexes and collect unbound proteins, application of the collected proteins to a Concanavalin A Sepharose column, and elution of glycoproteins from the column (two-step affinity chromatography). The glycoproteins isolated from the ovarian cancer patient blood serum were coated on microtiter plates and reacted with the antibodies purified from the ovarian cancer patient ascites fluid. Enzyme-conjugated antihuman IgG and substrate were added, and immunocomplexes detected by measuring absorbance.

Applicants respectfully submit that the Rao abstract and the Rao paper fail to disclose antibodies directed to an epitope of a cancer-associated marker protein and certainly fail to disclose antibodies to a cancer-associated marker protein that is a **modified form of a wild-type protein** as claimed in the amended claims.

The antibodies isolated from the ascites fluid of patients with ovarian epithelial cancer are used in the Rao abstract in an immunoassay to identify levels of unknown protein in the sera of the following groups of patients: patients with ovarian cancer (n = 10), healthy individuals (n = 2), patients with cervical dysplasia (n = 3), patients with squamous cell carcinoma (n = 3), patient with vaginitis (n = 1) and patient with Brenner tumor (n = 1). No control samples are provided to exclude antibody cross-reactivity with benign proteins. In addition, no control samples are provided to determine whether the antibodies are specific for particular tissues. The isolated patient antibodies could be reacting with <u>any</u> protein in the patient sample and are not specific for a cancer-associated marker protein as claimed in the present application. A similar experiment is described in the Rao paper, which reacts proteins isolated from the sera of 10 patients with serous cystadenocarcinoma and proteins isolated from the sera of 12 control patients with antibodies isolated from dissociated IgG complexes from ascitic fluid from the sera of ovarian epithelial cancer patients. Once again, no controls are provided to exclude antibody cross-reactivity with benign proteins and no tissue specificity is demonstrated. The isolated antibodies could be reacting with **any** protein in the sample and certainly lack specificity for a cancer-

associated marker protein that is a **modified form of a wild-type protein** as claimed in the amended claims of the present application.

In addition, applicants respectfully submit that the Rao paper and Rao abstract fail to provide a disclosure that is sufficiently complete and detailed to enable one of ordinary skill to make and use antibodies in an immunoassay. As such, the Rao references are not enabling and cannot provide the necessary disclosure for a proper 102(b) rejection. On the contrary, applicants have clearly described and enabled novel, highly sensitive and specific autoantibodies for detecting cancer-associated markers in a sample of bodily fluid from an individual expressing these markers. The claimed autoantibodies and methods of use could not have been developed from the inadequate teachings of the Rao references. The Rao abstract and the Rao paper fail to identify the "antigen" to be detected and fail to describe the patient or patients from whom the antibodies are obtained. Therefore, the Rao references provide no evidence that the antibodies can distinguish cancer-associated marker proteins from benign marker proteins.

Failure to Identify Antigen

Applicants respectfully submit that the Rao abstract and the Rao paper fail to provide sufficient technical teaching to enable one skilled in the art to isolate autoantibodies and perform assays to obtain meaningful results, especially in a diagnostic context, because Rao fails to identify the antigen with which the antibody is reactive.

A skilled reader seeking to carry out the teaching of Rao would be required to prepare antibodies using only the sparse teaching provided by Rao. Because Rao fails to identify the nature of the antigen, one would have no way of testing preparations of IgG isolated from patients in order to determine whether or not they contain an antibody equivalent to that tested by Rao. Rao provides no point of reference to allow one to determine whether one has antibodies of the "correct" specificity. Accordingly, there is serious doubt as to whether the skilled reader could reliably and reproducibly prepare autoantibodies having the required specificity without undue experimentation and burden.

Failure to Describe Antibodies

The Rao references describe the purification of antibodies from patients with cystadenocarcinoma of the ovary and combines the antibodies with serum samples from various patient groups. Rao fails to describe whether antibodies from all ovarian cancer patients were pooled or if antibodies from each individual patient were used. This alone makes the data set forth in the Rao paper insufficient to enable one skilled in the art to repeat the assay, particularly in a diagnostic context. If individual patient antibodies were used, then it is not clear which antibodies from which individuals were tested, and whether antibodies from different patients gave different results. Furthermore, there is no indication in the Rao paper as to how many patients with ovarian cancer had antibodies. It is quite possible that only one patient sample contained antibodies. If less than all patients produce antibodies, or have antibodies of appropriate specificity, then one cannot determine whether a patient sample used as a starting material for isolation of the antibodies actually contains antibody suitable for use as an assay reagent. Since the protein to be detected in either the Rao abstract or the Rao paper is unknown, there is no way of testing patient samples at any stage of the purification process for the presence of the desired antibody.

One of ordinary skill in the art would be unable to use the teachings of the Rao abstract or the Rao paper to prepare antibody reliably and reproducibly without undue burden. As such, the Rao paper and abstract fail to provide an enabling disclosure of autoantibodies specific for an epitope of a cancer-associated marker protein.

For at least the foregoing reasons, applicants respectfully submit that the claimed method is novel over both the Rao abstract and the Rao paper and request that the rejections under 35 U.S.C. §102 be withdrawn.

Rejections under 35 U.S.C. §103

Claims 1, 63, and 64 have been rejected under 35 U.S.C. §103(a) as being obvious over the Rao abstract in view of Voet & Voet (Biochemistry, John Wiley & Sons,

New York, 1990; "Voet"). Applicants traverse the rejection as applied to the claims as amended.

The Rao abstract and the Rao paper have been discussed above.

Voet discloses immobilization of antibodies on a solid surface. Voet fails to overcome the deficiencies of the Rao abstract and the Rao paper, because Voet fails to provide any additional guidance that would enable one skilled in the art to prepare autoantibodies equivalent to those tested in either Rao reference. Therefore, applicants respectfully request withdrawal of this rejection.

Claims 1 and 63-65 have been rejected under 35 U.S.C. §103(a) as being obvious over the Rao abstract in view of Voet and United States Patent No. 5,157,020 ("Kay"). Applicants traverse the rejection as applied to the claims as amended.

The Rao abstract, the Rao paper and Voet have been discussed above.

Kay discloses competitive inhibition assays. However, Kay fails to overcome the deficiencies of the Rao abstract, the Rao paper and Voet, because Kay fails to provide any additional guidance which would enable one skilled in the art to prepare autoantibodies equivalent to those tested in either Rao reference. Therefore, applicants respectfully request withdrawal of this rejection.

Claims 1, 2, 55-58, and 61 have been rejected under 35 U.S.C. §103(a) as being obvious over the Rao abstract in view of Gourevitch and Petrarca. Applicants traverse the rejection as applied to the claims as amended.

The Rao abstract, and the Rao paper have been discussed above.

Gourevitch and Petrarca were discussed in the interview with the Examiner on October 7, 2004. Gourevitch teach the use of monoclonal antibodies for the detection of tumor marker proteins. Petrarca discloses the epitope mapping of anti-MUC-1 antibodies to identify epitopes to use as vaccines for cancer treatment.

The claimed autoantibodies were clearly distinguished over Gourevitch and Petrarca in the October 7, 2004 interview, and the rejection was withdrawn. The additional disclosures by the Rao abstract and the Rao paper fail to make up for the deficiencies of Gourevitch and Petrarca. The Rao abstract and the Rao paper do not contain any disclosures which would lead one skilled in the art to conclude or even suspect that autoantibodies react with cancer-associated marker proteins as claimed. The disclosures of the Rao abstract and the Rao paper fail to contradict the arguments presented in the interviews with the Examiner or in the Declaration by Dr. Robertson filed November 23, 2004 that the autoantibodies of the claimed methods have high sensitivities and specificities. One of ordinary skill in the art would not be motivated to combine these references with a reasonable expectation of success to arrive at the claimed methods. Therefore, applicants respectfully request withdrawal of this rejection.

The Houghton paper

During the interview on June 6, 2005, the Examiner provided applicants with a newly cited prior art reference, the scientific paper of Houghton *et al.*, entitled "Detection of Cell Surface and Intracellular Antigens by Human Monoclonal Antibodies" *J. Exp. Med.* 158:53-65, 1983, ("the Houghton paper"), and requested that applicants distinguish the claimed method over the teachings of the Houghton paper. A copy of this paper is disclosed in the attached Supplemental Information Disclosure Statement.

Applicants respectfully submit that the Houghton paper describes the production of human monoclonal antibodies using hybridoma methodology. The Houghton paper fails to describe autoantibodies to a cancer-associated marker protein that is a modified form of a wild-type protein as claimed in the amended claims of the present application.

In the Houghton paper, a cell line, designated Ma4, was established and found to secrete IgM and IgG monoclonal antibodies specific for a surface antigen of human cells. The antibodies produced by the Ma4 cell line were reactive with a heat stable, trypsin and proteinase K-resistant cell surface antigen, referred to by Houghton as the "Ma4 antigen". Houghton produced five additional hybridoma cell lines that secreted monoclonal antibodies, namely M307, M311, M304, M305, and M54. Applicants respectfully submit that the data

provided in the Houghton paper fail to demonstrate selectivity of any of the antibodies for cancer-associated marker proteins over normal proteins and fail to demonstrate specificity for the specific type of cancer from which the hybridoma cell line was derived.

As explained in the Supplemental Amendment and Declaration Under 37 C.F.R. §1.132 by John Robertson, both filed on November 23, 2004 in the present application, the Examples and comparative data provided in Figures 1 and 2 of the present specification and the data submitted in the Declaration demonstrate that claimed autoantibodies have high sensitivities and affinities for various cancer-associated marker proteins. Applicants unexpectedly discovered that the claimed autoantibodies are specific for cancer-associated marker proteins, are able to distinguish between normal and pathological isoforms of a tumor marker protein, and display a high affinity for cancer-associated marker protein with little or no affinity for normal protein, thereby providing a sensitive tumor marker assay that can detect small amounts of cancer that might not be detectable by conventional methods.

For at least the foregoing reasons, applicants respectfully submit that the claims of the present application are novel and non-obvious in view of the Houghton paper.

Allowance of Corresponding European Patent Application

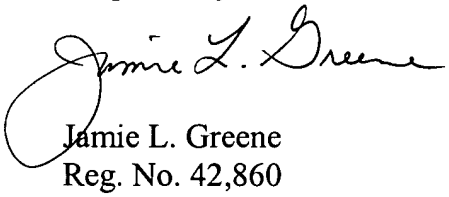
Applicants wish to bring to the Examiner's attention the fact that the corresponding European Patent Application (EP 99 959 578.8) was allowed by the European Patent Office on June 21, 2005. A copy of the Communication under Rule 51(4) EPC and a copy of the claims as amended are attached as Exhibit A. Applicants note that the allowed claims in the European Patent Application contain language that corresponds to the amendments to the claims presented in this Amendment and Response to Office Action.

CONCLUSION

Applicants respectfully submit that the pending claims define novel and patentable subject matter and provide a complete response to the Office Action. Accordingly, applicants respectfully request allowance of these claims. No additional fees are believed due, however, the Commissioner is hereby authorized to charge any deficiencies which may be required, or credit any overpayment, to Deposit Account Number 11-0855.

Early and favorable consideration is earnestly solicited. If the Examiner believes any informalities remain in the application that can be resolved by telephone interview, a telephone call to the 1-4 and 52-68 is respectfully solicited.

Respectfully submitted,



Jamie L. Greene
Reg. No. 42,860

KILPATRICK STOCKTON LLP
1100 Peachtree Street
Suite 2800
Atlanta, Georgia 30309-4530
Tel. (404) 815-6500
Attorney Docket No. 02332-0020 (49409-264826)

EPA/EPO/OEB
D-80298 München

+49 89 2399-0
TX 523 656 epmu d
FAX +49 89 2399-4465

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Baldock, Sharon Claire
BOULT WADE TENNANT,
Verulam Gardens
70 Gray's Inn Road
London WC1X 8BT
ROYAUME-UNI

Application No.	Ref.	Date
99 959 578.8 - 1223	SCB/51598/006	21.06.2005
Applicant: THE UNIVERSITY OF NOTTINGHAM		

Communication under Rule 51(4) EPC

You are informed that the Examining Division intends to grant a European patent on the basis of the above application with the text and drawings as indicated below:

In the text for the Contracting States:
AT BE CH CY DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE

Description, Pages

1-3, 5-20	as originally filed
4	received on 03.03.2004 with letter of 02.03.2004
3a	received on 22.04.2005 with letter of 20.04.2005

Claims, Numbers

1-30, 44 (part), 45-47	received on 03.03.2004 with letter of 02.03.2004
31-43, 44 (part)	received on 22.04.2005 with letter of 20.04.2005

Drawings, Sheets

1/8-8/8	as originally filed

With the following amendments to the above-mentioned documents according to your request dated 04.05.2005 :

Claims, Numbers	1*,20*,30*,40*

Comments

* As agreed during a telephone conversation with Nina White on 04.05.2005.

Registered Letter
EPO Form 2004 04.05CSX

Exhibit A

Druckexemplar

CLAIMS:

1. An *in vitro* method for detecting a cancer-associated marker protein present in a bodily fluid of a mammal which method comprises the steps of:

(a) contacting a sample of bodily fluid from said mammal with antibodies directed against at least one epitope of said marker protein; and

(b) detecting the presence of any complexes formed between said antibodies and any marker protein present in said sample;

wherein said antibodies are mammalian autoantibodies to said cancer-associated marker protein which are derived from the same species as the mammal from which said sample has been obtained, (and wherein said cancer-associated marker protein is a modified form of a wild-type protein)

2. A method as claimed in claim 1 wherein said sample is from a mammal substantially asymptomatic for pre-neoplasia or cancer.

3. A method as claimed in claim 1 wherein said sample is from a mammal symptomatic for cancer.

4. A method as claimed in claim 1 wherein said sample is from a mammal which has received therapy for cancer.

5. A method as claimed in any preceding claim wherein the mammal is a human and the autoantibodies are human autoantibodies.

6. A method as claimed in any preceding claim wherein said bodily fluid is plasma, serum, whole blood, urine, faeces, lymph, cerebrospinal fluid or nipple aspirate.

7. A method as claimed in any preceding claim wherein said cancer-associated marker protein is associated with lymphomas, leukaemias, breast cancers, colorectal cancers, lung cancers, pancreatic cancers, prostate cancers, cervical cancers, ovarian cancers, endometrial cancers or cancers of the skin.

8. A method as claimed in claim 7 wherein said cancer-associated marker protein is a breast cancer-associated marker protein.

9. A method as claimed in any preceding claim wherein said cancer-associated marker protein is a cancer-associated form of MUC1, BRCA1, p53, c-myc c-erbβ2 or Ras protein.

10. A method as claimed in claim 8 wherein said cancer-associated marker protein is a cancer-associated form of MUC1, BRCA1, BRCA2, p53, c-myc, c-erbβ2 or Ras protein associated with primary breast cancer.

11. A method as claimed in claim 8 wherein said cancer-associated marker protein is a cancer-associated form of MUC1, BRCA1, BRCA2, p53, c-myc, c-erbβ2 or Ras protein associated with advanced breast cancer.

12. A method as claimed in claim 10 wherein said autoantibodies are obtainable from monocytes isolated from a patient with primary breast cancer.

13. A method as claimed in claim 11 wherein said autoantibodies are obtainable from monocytes isolated from a patient with advanced breast cancer.

14. A method as claimed in any preceding claim wherein said autoantibodies are produced by an immortalized cell or cell population.

15. A method as claimed in any one of claims 1 to 14 wherein said autoantibodies are polyclonal antibodies.

16. A method as claimed in any preceding claim wherein said autoantibodies are immobilized on a solid surface.

17. A method as claimed in claim 16 wherein any complexes formed between said autoantibodies and any cancer-associated marker protein present in said sample are detected using secondary antibodies or autoantibodies specific for at least one epitope of said marker protein, said secondary autoantibodies carrying a detectable label.

18. A method as claimed in claim 16 wherein in addition to said sample a labelled cancer-associated marker protein is added carrying at least one epitope recognised by said autoantibodies.

19. Use of a method as claimed in any one of claims 1 to 18 to screen for recurrence of cancer after a treatment, to monitor systemic therapies or to select therapies.

20. A diagnostic reagent which comprises mammalian autoantibodies with a specificity for at least one epitope of a mammalian cancer-associated marker protein (wherein said cancer-associated marker protein is a modified form of a wild-type protein.)

21. A diagnostic reagent as claimed in claim 20 for use in detecting the presence of a mammalian cancer-associated marker protein in a sample of body fluid.

22. A reagent as claimed in claim 20 or claim 21 wherein said autoantibodies are human autoantibodies and said marker protein is a human cancer-associated marker protein.

23. A reagent as claimed in any one of claims 21 or 22 wherein said autoantibodies have specificity for at least one epitope of a cancer-associated marker protein associated with lymphomas, leukaemias, breast cancers, colorectal cancers, lung cancers, pancreatic cancers, prostate cancers, cervical cancers, ovarian cancers, endometrial cancers or cancers of the skin.

24. A reagent as claimed in claim 23 wherein said autoantibodies have specificity for at least one epitope of a breast cancer-associated marker protein.

25. A reagent as claimed in any one of claims 20 to 24 wherein said marker protein is a cancer-associated form of MUC1, BRCA1, BRCA2, p53, c-myc, c-erbβ2 or Ras protein.

26. A reagent as claimed in claim 24 wherein said marker protein is a cancer-associated form of MUC1, BRCA1, BRCA2, p53, c-myc, c-erbβ2 or Ras protein associated with primary breast cancer.

27. A reagent as claimed in claim 24 wherein said marker protein is a cancer-associated form of MUC1, BRCA1, BRCA2, p53, c-myc, c-erbβ2 or Ras protein associated with advanced breast cancer.

28. A reagent as claimed in claim 26 wherein said autoantibodies are obtainable from monocytes isolated from a patient with primary breast cancer.

29. A reagent as claimed in claim 27 wherein said autoantibodies are obtainable from monocytes isolated from a patient with advanced breast cancer.

30. An immortalized cell population capable of producing autoantibodies directed against at least one epitope of a mammalian cancer-associated marker protein(, wherein said cancer-associated marker protein is a modified form of a wild-type protein.)

31. An immortalized cell population as claimed in claim 30 which is capable of producing autoantibodies directed against at least one epitope of a human cancer-associated marker protein.

32. An immortalized cell population as claimed in claim 31 or claim 32 wherein said autoantibodies are directed against at least one epitope of a cancer-associated marker protein associated with lymphomas, leukaemias, breast cancers, colorectal cancers, lung cancer, pancreatic cancers, prostate cancers, cervical cancers, ovarian cancers, endometrial cancers or cancers of the skin.

33. An immortalised cell population as claimed in claim 32 wherein said autoantibodies are directed against an epitope of a breast cancer-associated marker protein.

34. An immortalized cell population as claimed in any one of claims 31 to 33 wherein said autoantibodies are directed against a cancer-associated form of MUC1, BRCA1, BRCA2, p53, c-myc, c-erbβ2 or Ras protein.

35. An immortalized cell population as claimed in claim 33 wherein said autoantibodies are autoantibodies to a cancer-associated form of MUC1, BRCA1, BRCA2, c-myc, p53, c-erbβ2 or Ras protein associated with primary breast cancer.

36. An immortalized cell population as claimed in claim 33 wherein said autoantibodies are autoantibodies to a cancer-associated form of MUC1, BRCA1, BRCA2, c-myc, c-erbβ2 or Ras protein associated with advanced breast cancer.

37. An immortalized cell population as claimed in anyone of claims 30 to 36 which is derived from B

lymphocytes isolated from a patient or a group of patients having cancer or other neoplasia.

38. An immortalised cell population as claimed in claim 35 wherein said cell population is derived from B lymphocytes of a patient or group of patients having primary breast cancer.

39. An immortalised cell population as claimed in claim 36 wherein said cell population is derived from B lymphocytes of a patient or group of patients with advanced breast cancer.

40. A kit for detecting a cancer-associated marker protein present in a bodily fluid of a mammal, the kit comprising:

(a) mammalian autoantibodies directed against a cancer-associated marker protein from the same species as said autoantibodies; and

(b) means for detecting the formation of complexes between said autoantibodies and said cancer-associated marker protein H H; (wherein said cancer-associated marker protein is a modified form of a wild-type protein.)

41. A kit as claimed in claim 40 wherein said autoantibodies are human autoantibodies

42. A kit as claimed in claim 40 or 41 wherein said autoantibodies are human autoantibodies.

43. A kit as claimed in any one of claims 40 to 42 wherein said marker protein is a cancer-associated marker protein associated with lymphomas, leukaemias, breast cancers, colorectal cancers, lung cancers, pancreatic cancers, prostate cancers, cervical cancers, ovarian cancers, endometrial cancers or cancers of the skin.

44. A kit as claimed in claim 43 wherein said

marker protein is a breast-cancer associated marker protein.

45. A kit as claimed in any one of claims 40 to 44 wherein said marker protein is a cancer-associated form of MUC1, BRCA1, BRCA2, p53, c-myc, c-erbβ2 or Ras protein.

46. A kit as claimed in claim 45 wherein said marker protein is a cancer-associated form of MUC1, BRCA1, BRCA2, c-myc, p53, c-erbβ2 or Ras protein associated with primary breast cancer.

47. A kit as claimed in claim 45 wherein said marker protein is a cancer-associated form of MUC1, BRCA1, BRCA2, p53, c-myc, c-erbβ2 or Ras protein associated with advanced breast cancer.

526054; MLM; SJW